

CLAIMS

What is claimed is:

1. A sustained release formulation comprising a therapeutically effective amount of at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate.

5 2. The sustained release formulation of claim 1, further comprising a pharmaceutically acceptable carrier.

3. The sustained release formulation of claim 1, wherein the antioxidant is a small-molecule antioxidant, or a pharmaceutically acceptable salt thereof, or an antioxidant enzyme.

10 4. The sustained release formulation of claim 3, wherein the small-molecule antioxidant is a hydralazine compound, a glutathione, a vitamin C, a vitamin E, a cysteine, a N-acetyl-cysteine, a β -carotene, an ubiquinone, an ubiquinol-10, a tocopherol, a coenzyme Q, or a mixture thereof.

15 5. The sustained release formulation of claim 3, wherein the antioxidant enzyme is superoxide dismutase, catalase, glutathione peroxidase, or a mixture thereof.

6. The sustained release formulation of claim 4, wherein the at least one antioxidant is a hydralazine compound or a pharmaceutically acceptable salt thereof.

7. The sustained release formulation of claim 6, wherein the at least one hydralazine compound is hydralazine hydrochloride.

20 8. The sustained release formulation of claim 7, wherein the hydralazine hydrochloride is present in an amount of about 30 milligrams to about 400 milligrams per day.

25 9. The sustained release formulation of claim 8, wherein the hydralazine hydrochloride is present in an amount of about 50 milligrams to about 300 milligrams per day.

10. The sustained release formulation of claim 1, wherein the isosorbide dinitrate is present in an amount of about 5 milligrams per day to about 200 milligrams per day.

11. The sustained release formulation of claim 10, wherein the isosorbide dinitrate is present in an amount of about 30 milligrams per day to about 160 milligrams per day.

30 12. The sustained release formulation of claim 1, wherein the isosorbide mononitrate is present in an amount of about 5 milligrams per day to about 120 milligrams per day.

13. The sustained release formulation of claim 12, wherein the isosorbide mononitrate is present in an amount of about 15 milligrams per day to about 100 milligrams per day.

14. The sustained release formulation of claim 1, wherein the formulation is an oral, parenteral or transdermal sustained release formulation.

15. The sustained release formulation of claim 14, wherein the transdermal sustained release formulation is a sustained-release patch.

16. The sustained release formulation of claim 14, wherein the oral sustained release formulation is a solid dose, a liquid dose or a suspension.

17. The sustained release formulation of claim 14, wherein the solid dose is a sustained-release tablet or a sustained release capsule.

18. The sustained release formulation of claim 1, comprising a therapeutically effective amount of hydralazine hydrochloride and isosorbide dinitrate.

19. The sustained release formulation of claim 1, comprising a therapeutically effective amount of hydralazine hydrochloride and isosorbide mononitrate.

20. The sustained release formulation of claim 1, further comprising at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated calcium channel blocker, nitrosated endothelin antagonist and nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or a mixture thereof.

21. The sustained release formulation of claim 1, further comprising at least one compound used to treat cardiovascular diseases, or a pharmaceutically acceptable salt thereof.

22. The sustained release formulation of claim 21, wherein the at least one compound used to treat cardiovascular diseases is an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, an endothelin antagonist, a renin inhibitor, or a mixture thereof.

23. A method of treating a vascular disease characterized by a nitric oxide insufficiency in a patient comprising administering to the patient the sustained release formulation of claim 1.

24. The method of claim 23, wherein the vascular disease characterized by nitric oxide insufficiency is a cardiovascular disease; a disease resulting from oxidative stress; low-renin hypertension; salt-sensitive hypertension; low-renin, salt-sensitive hypertension; primary pulmonary hypertension; thromboembolic pulmonary hypertension; pregnancy-

induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal disease; heart failure; microvascular cardiac ischemia; left ventricular hypertrophy with disproportionate microvascularization or diastolic dysfunction.

25. The method of claim 24, wherein the cardiovascular disease is congestive
5 heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal) angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient
10 ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia or bleeding disorders.

26. The method of claim 25, wherein the cardiovascular disease is congestive
15 heart failure, hypertension, restenosis or atherosclerosis.

27. The method of claim 24, wherein the disease resulting from oxidative stress is atherogenesis, atheromatosis, arteriosclerosis, atherosclerosis, vascular hypertrophy associated with hypertension, hyperlipoproteinaemia, normal vascular degeneration through aging, parathyroidal reactive hyperplasia, chronic renal disease, a neoplastic disease, an
20 inflammatory disease, a neurological and acute bronchopulmonary disease, a tumorigenesis, an ischemia-reperfusion syndrome, arthritis or sepsis.

28. A method of treating Raynaud's syndrome in a patient comprising administering to the patient the sustained release formulation of claim 1.

29. An orally administerable composition comprising about 37.5 mg hydralazine
25 hydrochloride and about 10 mg isosorbide dinitrate or about 37.5 mg hydralazine hydrochloride and about 20 mg isosorbide dinitrate.

30. An orally administerable composition comprising about 75 mg hydralazine hydrochloride and about 20 mg isosorbide dinitrate or about 75 mg hydralazine hydrochloride and about 40 mg isosorbide dinitrate.

31. The orally administerable composition of claim 29 or 30, wherein the
30 hydralazine and the isosorbide dinitrate are a solid dose, a liquid dose or a suspension.

32. The orally administerable composition of claim 31, wherein the solid dose is a tablet or a capsule.

33. The orally administerable composition of claim 32, wherein the capsule is a sustained release capsule.

34. The orally administerable composition of claim 32, wherein the tablet is a sustained-release tablet, a sublingual tablet or a chewable tablet.

5 35. The orally administerable composition of claim 29 or 30, further comprising at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated calcium channel blocker, nitrosated endothelin antagonist and nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or a mixture thereof.

10 36. The orally administerable composition of claim 29 or 30, further comprising at least one compound used to treat cardiovascular diseases, or a pharmaceutically acceptable salt thereof.

15 37. The orally administerable composition of claim 29 or 30, wherein the at least one compound used to treat cardiovascular diseases is an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, an endothelin antagonist, a renin inhibitor, or a mixture thereof.

38. A method of treating a vascular disease characterized by a nitric oxide insufficiency in a patient comprising administering to the patient the orally administerable composition of claims 29 or 30 at least once per day to at least four times per day.

20 39. The method of claim 38, wherein the vascular disease characterized by nitric oxide insufficiency is a cardiovascular disease; a disease resulting from oxidative stress; low-renin hypertension; salt-sensitive hypertension; low-renin, salt-sensitive hypertension; primary pulmonary hypertension; thromboembolic pulmonary hypertension; pregnancy-induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal disease; heart failure; microvascular cardiac ischemia; left ventricular hypertrophy with disproportionate microvascularization or diastolic dysfunction.

25 40. The method of claim 39, wherein the cardiovascular disease is congestive heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal) angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation,

vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia or bleeding disorders.

5 41. The method of claim 40, wherein the cardiovascular disease is congestive heart failure, hypertension, restenosis or atherosclerosis.

 42. The method of claim 39, wherein the disease resulting from oxidative stress is atherogenesis, atheromatosis, arteriosclerosis, atherosclerosis, vascular hypertrophy associated with hypertension, hyperlipoproteinaemia, normal vascular degeneration through aging, parathyroidal reactive hyperplasia, chronic renal disease, a neoplastic disease, an
10 inflammatory disease, a neurological and acute bronchopulmonary disease, a tumorigenesis, an ischemia-reperfusion syndrome, arthritis or sepsis.

 43. A method of treating Raynaud's syndrome in a patient comprising administering to the patient the orally administerable composition of claims 29 or 30 at least once per day to at least four times per day.

15 44. A method of treating and/or preventing a vascular disease characterized by nitric oxide insufficiency in a patient comprising administering to the patient a therapeutically effective amount of at least one antioxidant, or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or
20 is a substrate for nitric oxide synthase or a pharmaceutically acceptable salt thereof.

 45. The method of claim 44, wherein the vascular disease characterized by nitric oxide insufficiency is a cardiovascular disease; a disease resulting from oxidative stress; low-renin hypertension; salt-sensitive hypertension; low-renin, salt-sensitive hypertension; primary pulmonary hypertension; thromboembolic pulmonary hypertension; pregnancy-induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal
25 disease; heart failure; microvascular cardiac ischemia; left ventricular hypertrophy with disproportionate microvascularization or diastolic dysfunction.

 46. The method of claim 44, further comprising administering a pharmaceutically acceptable carrier.

30 47. The method of claim 45, wherein the cardiovascular disease is congestive heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal)

angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia or bleeding disorders.

48. The method of claim 47, wherein the cardiovascular disease is congestive heart failure, hypertension, restenosis or atherosclerosis.

49. The method of claim 45, wherein the disease resulting from oxidative stress is atherogenesis, atheromatosis, arteriosclerosis, atherosclerosis, vascular hypertrophy associated with hypertension, hyperlipoproteinaemia, normal vascular degeneration through aging, parathyroidal reactive hyperplasia, chronic renal disease, a neoplastic disease, an inflammatory disease, a neurological and acute bronchopulmonary disease, a tumorigenesis, an ischemia-reperfusion syndrome, arthritis or sepsis.

50. The method of claim 44, wherein the antioxidant is a small-molecule antioxidant, or a pharmaceutically acceptable salt thereof, or an antioxidant enzyme.

51. The method of claim 50, wherein the small-molecule antioxidant is a hydralazine compound, a glutathione, a vitamin C, a vitamin E, a cysteine, a N-acetylcysteine, a β -carotene, an ubiquinone, an ubiquinol-10, a tocopherol, a coenzyme Q, or a mixture thereof.

52. The method of claim 50, wherein the antioxidant enzyme is a superoxide dismutase, a catalase, a glutathione peroxidase, or a mixture thereof.

53. The method of claim 51, wherein the hydralazine compound is budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine or todralazine or a pharmaceutically acceptable salt thereof.

54. The method of claim 53, wherein the hydralazine compound is hydralazine hydrochloride.

55. The method of claim 54, wherein the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 400 milligrams per day.

56. The method of claim 55, wherein the hydralazine hydrochloride is administered in an amount of about 50 milligrams per day to about 300 milligrams per day.

57. The method of claim 44, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or

endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

58. The method of claim 57, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione or S-nitroso-cysteinyl-glycine.

59. The method of claim 57, wherein the S-nitrosothiol is:

(i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;

(ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; and

(iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylaryl amino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, an alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q, or $-(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T}-\text{Q}$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, $-\text{S}(\text{O})_o-$ or $-\text{N}(\text{R}_a)\text{R}_i-$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$, or $-(\text{N}_2\text{O}_2-)\cdot\text{M}^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$ or $-(\text{N}_2\text{O}_2-)\cdot\text{M}^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

60. The method of claim 44, wherein the at least one compound that donates,

transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or inhibitors of the enzyme arginase.

61. The method of claim 44, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

- (i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;
- (ii) a compound that comprises at least one O₂N-O-, O₂N-N-, O₂N-S- or -O₂N-C- group;
- (iii) a N-oxo-N-nitrosoamine having the formula: R¹R²-N(O-M⁺)-NO, wherein R¹ and R² are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M⁺ is an organic or inorganic cation.

62. The method of claim 61, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

63. The method of claim 61, wherein compound comprising at least one O₂N-O-, O₂N-N-, O₂N-S- or O₂N-C- group is an O₂N-O-polypeptide, an O₂N-N-polypeptide, an O₂N-S-polypeptide, an O₂N-C-polypeptide, an O₂N-O-amino acid, O₂N-N-amino acid, O₂N-S-amino acid, an O₂N-C-amino acid, an O₂N-O-sugar, an O₂N-N-sugar, O₂N-S-sugar, an O₂N-C-sugar, an O₂N-O-oligonucleotide, an O₂N-N-oligonucleotide, an O₂N-S-oligonucleotide, an O₂N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-O-hydrocarbon, a straight or branched, saturated

or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-C-hydrocarbon, an O₂N-O-heterocyclic compound, an O₂N-N-heterocyclic compound, an O₂N-S-heterocyclic compound or an O₂N-C-heterocyclic compound.

64. The method of claim 63, wherein compound comprising at least one O₂N-O-, O₂N-N-, O₂N-S- or O₂N-C- group is isosorbide mononitrate and/or isosorbide dinitrate.

65. The method of claim 64, wherein the isosorbide dinitrate is administered in an amount of about 5 milligrams per day to about 200 milligrams per day.

66. The method of claim 65, wherein the isosorbide dinitrate is administered in an amount of about 30 milligrams per day to about 160 milligrams per day.

67. The method of claim 64, wherein the isosorbide mononitrate is administered in an amount of about 5 milligrams per day to about 120 milligrams per day.

68. The method of claim 67, wherein the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 100 milligrams per day.

69. The method of claim 44, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase or a pharmaceutically acceptable salt thereof, are administered orally, parenterally or transdermally.

70. The method of claim 69, wherein the transdermal administration is a sustained-release patch.

71. The method of claim 69, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase or a pharmaceutically acceptable salt thereof, are administered orally.

72. The method of claim 71, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase or a pharmaceutically acceptable salt thereof, are administered orally as a solid dose, a liquid dose or a suspension.

73. The method of claim 72, wherein the solid dose is a tablet or capsule.

74. The method of claim 72, wherein the solid dose is a sustained release capsule or a sustained release tablet.
75. The method of claim 73, wherein the tablet or capsule is a sublingual tablet or a sublingual capsule.
- 5 76. The method of claim 73, wherein the tablet or capsule is a chewable tablet or a chewable capsule.
77. The method of claim 44, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric
10 oxide synthase are administered as components of the same composition.
78. The method of claim 44, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase are administered to the patient as separate components.
- 15 79. The method of claim 78, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase are administered to the patient as separate components at about the same time.
80. The method of claim 44, further comprising administering a digitalis.
- 20 81. The method of claim 80, wherein the digitalis is digoxin
82. The method of claim 81, wherein the digoxin is administered in an amount to achieve a blood serum concentration of at least about 0.7 nanograms per milliliter to about 2.0 nanograms per milliliter.
83. The method of claim 44, further comprising administering a therapeutically
25 effective edema managing amount of a diuretic compound.
84. The method of claim 83, wherein the diuretic compound is a thiazide, ethacrynic acid, a furosemide, a spiranolactone, a triamterene, or a mixture thereof.
85. The method of claim 83, further comprising administering a therapeutically effective amount of potassium.
- 30 86. The method of claim 85, wherein the potassium is administered as potassium chloride or by the daily ingestion of foods with high potassium content.
87. The method of claim 44, further comprising administering at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker,

nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or a mixture thereof.

88. The method of claim 44, further comprising administering at least one compound used to treat cardiovascular diseases, or a pharmaceutically acceptable salt thereof.

5 89. The method of claim 88, wherein the at least one compound used to treat cardiovascular diseases is an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, an endothelin antagonist, a renin inhibitor, or a mixture thereof.

10 90. The method of claim 44, wherein the at least one antioxidant is hydralazine hydrochloride and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is isosorbide dinitrate and/or isosorbide mononitrate.

15 91. A method of treating Raynaud's syndrome in a patient comprising administering to the patient a therapeutically effective amount of at least one antioxidant, or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase or a pharmaceutically acceptable salt thereof.

20 92. The method of claim 91, further comprising administering a pharmaceutically acceptable carrier.

93. The method of claim 91, wherein the antioxidant is a small-molecule antioxidant, or a pharmaceutically acceptable salt thereof, or an antioxidant enzyme.

25 94. The method of claim 93, wherein the small-molecule antioxidant is a hydralazine compound, a glutathione, a vitamin C, a vitamin E, a cysteine, a N-acetylcysteine, a β -carotene, an ubiquinone, an ubiquinol-10, a tocopherol, a coenzyme Q, or a mixture thereof.

95. The method of claim 93, wherein the antioxidant enzyme is a superoxide dismutase, a catalase, a glutathione peroxidase, or a mixture thereof.

30 96. The method of claim 94, wherein the hydralazine compound is budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine or todralazine or a pharmaceutically acceptable salt thereof.

97. The method of claim 96, wherein the hydralazine compound is hydralazine hydrochloride.

98. The method of claim 97, wherein the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 400 milligrams per day.

99. The method of claim 98, wherein the hydralazine hydrochloride is administered in an amount of about 50 milligrams per day to about 300 milligrams per day.

100. The method of claim 91, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

101. The method of claim 100, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione or S-nitroso-cysteinyl-glycine.

102. The method of claim 100, wherein the S-nitrosothiol is:

(i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;

(ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; and

(iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylaryl amino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, an alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q, or $-(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T}-\text{Q}$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_a)R_i-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an

alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$, or $-(\text{N}_2\text{O}_2^-)\cdot\text{M}^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$ or $-(\text{N}_2\text{O}_2^-)\cdot\text{M}^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

103. The method of claim 91, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or inhibitors of the enzyme arginase.

104. The method of claim 91, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

- (i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;
- (ii) a compound that comprises at least one $\text{O}_2\text{N-O-}$, $\text{O}_2\text{N-N-}$, $\text{O}_2\text{N-S-}$ or $-\text{O}_2\text{N-C-}$ group;
- (iii) a N-oxo-N-nitrosoamine having the formula: $\text{R}^1\text{R}^2\text{-N}(\text{O-M}^+)\text{-NO}$, wherein R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

105. The method of claim 104, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

106. The method of claim 104, wherein compound comprising at least one $\text{O}_2\text{N-O-}$,

O₂N-N-, O₂N-S- or O₂N-C- group is an O₂N-O-polypeptide, an O₂N-N-polypeptide, an O₂N-S-polypeptide, an O₂N-C-polypeptide, an O₂N-O-amino acid, O₂N-N-amino acid, O₂N-S-amino acid, an O₂N-C-amino acid, an O₂N-O-sugar, an O₂N-N-sugar, O₂N-S-sugar, an O₂N-C-sugar, an O₂N-O-oligonucleotide, an O₂N-N-oligonucleotide, an O₂N-S-oligonucleotide,
5 an O₂N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-C-hydrocarbon, an O₂N-O-heterocyclic
10 compound, an O₂N-N-heterocyclic compound, an O₂N-S-heterocyclic compound or an O₂N-C-heterocyclic compound.

107. The method of claim 106, wherein compound comprising at least one O₂N-O-, O₂N-N-, O₂N-S- or O₂N-C- group is isosorbide mononitrate and/or isosorbide dinitrate.

15 108. The method of claim 107, wherein the isosorbide dinitrate is administered in an amount of about 5 milligrams per day to about 200 milligrams per day.

109. The method of claim 108, wherein the isosorbide dinitrate is administered in an amount of about 30 milligrams per day to about 160 milligrams per day.

20 110. The method of claim 107, wherein the isosorbide mononitrate is administered in an amount of about 5 milligrams per day to about 120 milligrams per day.

111. The method of claim 110, wherein the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 100 milligrams per day.

25 112. The method of claim 91, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase are administered orally, parentally or transdermally.

113. The method of claim 112, wherein the transdermal administration is a sustained-release patch.

30 114. The method of claim 91, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase are administered orally.

115. The method of claim 114, wherein the oral administration is a solid, a liquid

dose or a suspension.

116. The method of claim 115, wherein the solid dose is a tablet or a capsule.

117. The method of claim 114, wherein the solid dose is a sustained-release tablet or a sustained release capsule.

5 118. The method of claim 116, wherein the tablet is a sublingual tablet or a chewable tablet.

119. The method of claim 91, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric
10 oxide synthase are administered as components of the same composition.

120. The method of claim 91, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric
oxide synthase are administered as separate components.

15 121. The method of claim 120, wherein the at least one antioxidant and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase are administered to the patient as separate components at about the same time.

20 122. The method of claim 91, further comprising administering at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or a mixture thereof.

25 123. A method of treating and/or preventing a vascular disease characterized by nitric oxide insufficiency in a patient comprising administering to the patient a therapeutically effective amount of at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or a mixture thereof.

30 124. The method of claim 123, further comprising administering a pharmaceutically acceptable carrier.

125. The method of claim 123, wherein the vascular disease characterized by nitric oxide insufficiency is a cardiovascular disease; a disease resulting from oxidative stress; low-renin hypertension; salt-sensitive hypertension; low-renin, salt-sensitive hypertension;

primary pulmonary hypertension; thromboembolic pulmonary hypertension; pregnancy-induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal disease; heart failure; microvascular cardiac ischemia; left ventricular hypertrophy with disproportionate microvascularization or diastolic dysfunction.

5 126. The method of claim 125, wherein the cardiovascular disease is congestive heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal) angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient
10 ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia or bleeding disorders.

15 127. The method of claim 126, wherein the cardiovascular disease is congestive heart failure, hypertension, restenosis or atherosclerosis.

 128. The method of claim 125, wherein the disease resulting from oxidative stress is atherogenesis, atheromatosis, arteriosclerosis, atherosclerosis, vascular hypertrophy associated with hypertension, hyperlipoproteinaemia, normal vascular degeneration through
20 aging, parathyroidal reactive hyperplasia, chronic renal disease, a neoplastic disease, an inflammatory disease, a neurological and acute bronchopulmonary disease, a tumorigenesis, an ischemia-reperfusion syndrome, arthritis or sepsis.

 129. The method of claim 123, wherein the at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated calcium channel
25 blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or mixture thereof, are in the form of a pharmaceutically acceptable salt.

 130. The method of claim 123, wherein the at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated calcium channel
30 blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or mixture thereof, are orally administered as a solid dose.

 131. The method of claim 130, wherein the solid dose is a tablet or capsule.

 132. The method of claim 131, wherein the capsule is a sustained release tablet or a

sustained release capsule

133. The method of claim 131, wherein the tablet is a sublingual tablet.

134. The method of claim 131, wherein the tablet is a chewable tablet.

5 135. The method of claim 123, wherein the at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or a mixture thereof, are administered transdermally.

136. The method of claim 135, wherein the transdermal application is a sustained-release patch.

10 137. The method of claim 123, further comprising administering at least one antioxidant, or a pharmaceutically acceptable salt thereof.

138. The method of claim 137, wherein the antioxidant is a small-molecule antioxidant, or a pharmaceutically acceptable salt thereof, or an antioxidant enzyme.

15 139. The method of claim 138, wherein the small-molecule antioxidant is a hydralazine compound, a glutathione, a vitamin C, a vitamin E, a cysteine, a N-acetylcysteine, a β -carotene, an ubiquinone, an ubiquinol-10, a tocopherol, a coenzyme Q, or a mixture thereof.

140. The method of claim 138, wherein the antioxidant enzyme is a superoxide dismutase, a catalase, a glutathione peroxidase, or a mixture thereof.

20 141. The method of claim 139, wherein the hydralazine compound is budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine or todralazine, or a pharmaceutically acceptable salt thereof.

142. The method of claim 141, wherein the hydralazine compound is hydralazine hydrochloride.

25 143. The method of claim 123, further comprising administering at least one compound used to treat cardiovascular diseases, or a pharmaceutically acceptable salt thereof.

144. The method of claim 143, wherein the at least one compound used to treat cardiovascular diseases is an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, an endothelin antagonist, a renin inhibitor, or a mixture thereof.

30 145. A transdermal patch comprising a therapeutically effective amount of at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate.

146. The transdermal patch of claim 145, further comprising a pharmaceutically acceptable carrier.

147. The transdermal patch of claim 145, wherein the antioxidant is a small-molecule antioxidant, or a pharmaceutically acceptable salt thereof, or an antioxidant enzyme.

148. The transdermal patch of claim 147, wherein the small-molecule antioxidant is a hydralazine compound, a glutathione, a vitamin C, a vitamin E, a cysteine, a N-acetylcysteine, a β -carotene, an ubiquinone, an ubiquinol-10, a tocopherol, a coenzyme Q, or a mixture thereof.

149. The transdermal patch of claim 147, wherein the antioxidant enzyme is superoxide dismutase, catalase, glutathione peroxidase, or a mixture thereof.

150. The transdermal patch of claim 148, wherein the at least one antioxidant is a hydralazine compound or a pharmaceutically acceptable salt thereof.

151. The transdermal patch of claim 150, wherein the at least one hydralazine compound is hydralazine hydrochloride.

152. The transdermal patch of claim 151, wherein the hydralazine hydrochloride is present in an amount of about 30 milligrams to about 400 milligrams per day.

153. The transdermal patch of claim 152, wherein the hydralazine hydrochloride is present in an amount of about 50 milligrams to about 300 milligrams per day.

154. The transdermal patch of claim 145, wherein the isosorbide dinitrate is present in an amount of about 5 milligrams per day to about 200 milligrams per day.

155. The transdermal patch of claim 154, wherein the isosorbide dinitrate is present in an amount of about 30 milligrams per day to about 160 milligrams per day.

156. The transdermal patch of claim 145, wherein the isosorbide mononitrate is present in an amount of about 5 milligrams per day to about 120 milligrams per day.

157. The transdermal patch of claim 156, wherein the isosorbide mononitrate is present in an amount of about 15 milligrams per day to about 100 milligrams per day.

158. The transdermal patch of claim 145, wherein the transdermal patch is a sustained-release transdermal patch.

159. The transdermal patch of claim 145, comprising a therapeutically effective amount of hydralazine hydrochloride and isosorbide dinitrate.

160. The transdermal patch of claim 145, comprising a therapeutically effective amount of hydralazine hydrochloride and isosorbide mononitrate.

161. The transdermal patch of claim 145, further comprising at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated calcium channel blocker, nitrosated endothelin antagonist and nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, or a mixture thereof.

5 162. The transdermal patch of claim 145, further comprising at least one compound used to treat cardiovascular diseases, or a pharmaceutically acceptable salt thereof.

163. The transdermal patch of claim 162, wherein the at least one compound used to treat cardiovascular diseases is an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II
10 receptor antagonist, an endothelin antagonist, a renin inhibitor, or a mixture thereof.

164. A method of treating a vascular disease characterized by a nitric oxide insufficiency in a patient comprising administering to the patient the transdermal patch of claim 145.

165. The method of claim 164, wherein the vascular disease characterized by nitric
15 oxide insufficiency is a cardiovascular disease; a disease resulting from oxidative stress; low-renin hypertension; salt-sensitive hypertension; low-renin, salt-sensitive hypertension; primary pulmonary hypertension; thromboembolic pulmonary hypertension; pregnancy-induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal disease; heart failure; microvascular cardiac ischemia; left ventricular hypertrophy with
20 disproportionate microvascularization or diastolic dysfunction.

166. The method of claim 165, wherein the cardiovascular disease is congestive heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal)
25 angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, pulmonary thromboembolism, cerebral thromboembolism,
30 thrombophlebitis, thrombocytopenia or bleeding disorders.

167. The method of claim 166, wherein the cardiovascular disease is congestive heart failure, hypertension, restenosis or atherosclerosis.

168. The method of claim 165, wherein the disease resulting from oxidative stress

is atherogenesis, atheromatosis, arteriosclerosis, artherosclerosis, vascular hypertrophy associated with hypertension, hyperlipoproteinaemia, normal vascular degeneration through aging, parathyroidal reactive hyperplasia, chronic renal disease, a neoplastic disease, an inflammatory disease, a neurological and acute bronchopulmonary disease, a tumorigenesis,
5 an ischemia-reperfusion syndrome, arthritis or sepsis.

169. A method of treating Raynaud's syndrome in a patient comprising administering to the patient the transdermal patch of claim 145.

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